III. REMARKS

A. Amendments to the Specification

Paragraph [0001] of the specification was amended to correct a typographical error in the filing date of the priority application.

A duplicate recitation of "steady state concentration" in the second to last sentence of paragraph [0123] was replaced with "elimination rate constant." Applicants note that loratadine's steady state concentration (i.e., 0.002 mcg/ml), loratadine's volume of distribution (i.e., 1,660,000 ml), loratadine's half-life (i.e., 8.4 hours) and loratadine's elimination rate constant (i.e., 0.693/half-life) were recited in the original paragraph [0123]. The product of the recited steady state, volume of distribution and elimination rate constant (i.e., 0.002 mcg/ml x 1,660,000 ml x (0.693/84 hours)) is about 274 mcg/hour. "274 mcg/hour" was also recited in the original paragraph [0123]. Accordingly, it is clear that "elimination rate constant" and not a duplicate "steady state concentration" was intended in the second to last sentence of paragraph [0123].

In the last sentence of paragraph [0123], "9.8 mcg/hour/cm^2" was replaced with "6.85 mcg/hour/cm^2," because "[d]ividing 274 mcg/hour/40 cm^2 by 40, yields a release rate of" "6.85 mcg/hour/cm^2", and not "9.8 mcg/hour/cm^2" as was recited in the original paragraph [0123]. To correct this arithmetical error, "9.8 mcg/hour/cm^2" was replaced with "6.85 mcg/hour/cm^2" in the last sentence of paragraph [0123].

It is respectfully submitted that these amendments are not new matter.

B. Status of the claims

Claims 8, 16, 20, 22, 30, 32, 46-49 were amended without prejudice. Support for the amendments can be found through out the specification. For example, support for "a plasma level of loratadine at steady state of about 3 ng/ml" can be found, e.g., in paragraphs [0023] reciting "a plasma level of loratadine at steady-state from about 1 to

about 3 ng/ml." Support for "transdermal delivery system surface area" can be found, e.g., in paragraph [0123], reciting "transdermal patch surface area." It is respectfully submitted that no new matter was introduced by virtue of these amendments.

Claims 8-11, 13, 14, 16, 20, 22-24, 29, 30, 32-38, and 40-55 are pending.

C. Rejection under 35 U.S.C. § 112

Claims 53-55 were rejected under 35 U.S.C. § 112, first paragraph, allegedly "as failing to comply with the written description requirement." *Office Action, page 2.* It was asserted that there is "no disclosure of the solution of loratadine to form a transdermal delivery device" in the present specification.

The rejection is respectfully traversed.

Paragraph [0109] of the specification recites that a loratadine solvent may be included in the transdermal delivery systems, and that solvents, preferably, "dissolve the loratadine to a sufficient extend thereby avoiding complete salt formation." Paragraphs [0148] and [0155] recite in part that "Loratadine is dissolved with ethanol and water and the solution is placed into the donor cell."

The specification therefore conveys to one skilled in the relevant art that the inventors at the time the application was filed had possession of a transdermal delivery device comprising a solution of loratadine, at the very least for the reasons articulated in the preceding paragraph.

Withdrawal of the rejection is respectfully requested.

D. Rejection under 35 U.S.C. § 103

Claims 8-11, 13, 14, 16, 20-24, 29, 30, 32-38, and 40-49 were rejected under 35 U.S.C. § 103 (a) over U.S. Patent No. 4,910,205 to Kogan et al. ("the Kogan reference") in combination with U.S. Patent No. 5,968,547 to Reder et al.

The rejection is respectfully traversed.

However, to advance prosecution and further differentiate over the cited references, independent claims 8, 20 and 46 (the only pending independent claims) were amended without prejudice to recite "a plasma level of loratadine at steady state of about 3 ng/ml."

The cited references do not teach or suggest maintaining a steady state plasma level of loratadine of about 3 ng/ml. In fact, steady state plasma levels of loratadine calculated from the flux at approximate steady state of the Kogan reference are different and do not overlap with the plasma level of loratatidne at steady state recited in the present claims.

The present specification describes two ways to calculate the dosing rate of loratadine (i.e., the amount of drug released per unit time from transdermal delivery system through the skin and into the bloodstream of a human patient). *See paragraph [0123].*

First, the specification states that the dosing rate is "a product of the steady state concentration of loratadine and a representative clearance rate." *See paragraph [0123].* In other words, according to the present specification, dosing rate= C_{ss} x CL, where C_{ss} is loratadine's steady-state concentration, and CL is loratadine's clearance rate. The steady-steady concentration of loratadine may therefore be calculated by dividing the dosing rate of loratadine by its clearance rate. In other words, C_{ss}=dosing rate/CL.

The "flux"[1] of the Final Gel of Table 1 of the Kogan reference (the highest flux listed in Table 1) is "2.26 mg/15 cm^2/day," or 94167 ng/hour (2.26/24x1000000=94167). The clearance rate of loratadine is 196000 ml/hr. *See paragraph [0123] of the present specification.* The calculated steady state loratadine concentration after administration of the Final Gel of Kogan at approximately steady state is therefore 0.48 ng/ml (94167/196000=0.48). This calculated steady state concentration does not overlap with the steady state concentration of "about 3 ng/ml" recited in independent claims 8, 20 and 46.

Similarly, calculating loratadine's steady state concentration after administration of the Final Gel of the Kogan reference by using the second formula described in the present specification does not overlap with the steady state concentration of "about 3 ng/ml" recited in the present claims. The present specification states that the dosing rate is equal to the "[t]he product of steady state concentration, volume of distribution and elimination rate constant." *See paragraph [0123].* The elimination rate constant is "0.693/half-life." *See Id.* In other words, the dosing rate= C_{ss} x V_d x 0.693/half-life, where C_{ss} is loratadine's steady state plasma concentration and V_d is its volume of distribution. The steady-steady concentration of loratadine may be calculated by dividing the dosing rate by the loratadine's volume of distribution and elimination rate constant. In other words, C_{ss}=dosing rate/(V_d x 0.693/half-life).

The dosing rate at approximate steady state after administration of the Final Gel of the Kogan reference is 2.26 mg/15cm^2/day, or 94167 ng/hour (2.26/24x1000000=94167). *See Table 1 of the Kogan reference.* According to the present specification, loratadine's V_d is 1660000 ml, and loratadine's half-life is 8.4 hours. *See paragraph [0123] of the present specification.* The calculated steady state loratadine concentration after administration of the Final Gel at approximately steady state of the Kogan reference is therefore 0.69 ng/ml (94167/(1660000x0.693/8.4))=0.69).

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[1] The "flux" of the Kogan reference is interchangeable with "dosing rate," because Kogan reference defines flux "as the amount of drug that traverse skin over time for a specified area." *Column 3, lines 30-31.*

This calculated steady state concentration of loratadine is in sharp contrast to the steady state concentration of "about 3 ng/ml" recited in independent claims 8, 20 and 46.

The cited references therefore do not teach or suggest maintaining loratadine steady state concentration of "about 3 ng/ml" as recited in independent claims 8, 20 and 46.

The Board of Patent Appeals and Interferences has recently issued a precedential opinion confirming that:

> … obviousness cannot be proven merely by showing that the elements of a claimed device were known in a prior art; it must be shown that those of ordinary skill in the art would have had some "apparent reason to combine the known elements in the fashion claimed …
> [Similarly,] obviousness cannot be proven merely by showing that a known composition could could have been modified by routine experimentation or solely on the expectation of success; it must be shown that those of ordinary skill in the art would have had some apparent reason to modify the known composition in a way that result in the claimed composition.

Appeal No. 2007-4423, Decision of Appeal dated July 23, 2008.

In the present case, there is no indication in the cited references that the release profile described in the Kogan reference is unacceptable, or the specific release profiles recited in the present claims are desirable.

The cited references do not therefore provide a reason to change the teachings of the cited references to arrive at the presently claimed release profiles, and do not render the present claims obvious. *Appeal No. 2007-4423, Decision of Appeal dated July 23, 2008.*

Applicants respectfully request that Examiner reconsiders arguments presented in the response filed on July 28, 2008, in view of the comments above.

Withdrawal of the rejection is respectfully requested.

IV. CONCLUSION

An early and favorable action on the merits is earnestly solicited. The Examiner is respectfully invited to contact the undersigned by telephone, if a telephone interview would advance prosecution of the present application.

Respectfully submitted,
DAVIDSON, DAVIDSON & KAPPEL, LLC

By: _____
Oleg Ioselevich
Reg. No. 56,963

DAVIDSON, DAVIDSON & KAPPEL, LLC
485 Seventh Avenue, 14th Floor
New York, New York 10018
(212) 736-1940